REMARKS

TELEPHONE CONFERENCE

Applicants gratefully acknowledge a telephone conference with Examiner Leary on January 7, 2004, during which the grounds for rejection presented in the November 28, 2003 Office Action ("Office Action") were discussed. Specifically, Applicants noted that the present invention is drawn to a method to detect ATP in a sample by reducing the steps of cell lysis, endogenous ATPase inhibition, substrate and luciferase addition *to a single step*, whereas methods of the prior art teach cell lysis and luciferase addition in multiple, sequential steps.

37 C.F.R. 1.132 DECLARATION TRAVERSING REJECTIONS

Pursuant to the telephone conference with the Examiner on January 7, 2004, Applicants have enclosed herewith a 37 C.F.R. 1.132 Declaration Traversing Rejections under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 (the "Declaration"), as discussed below. The Declaration is signed by inventor Keith Wood. Applicants respectfully assert that the arguments below, and the Declaration enclosed herewith, provide independent grounds overcoming the Examiner's rejections under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 in the Office Action.

THE INVENTION

The present invention is drawn to a method "to detect ATP in a sample by reducing the steps of cell lysis, endogenous ATPase inhibition, and substrate and luciferase addition *to a single step*." Specification, page 4, lines 10-12 (*emphasis added*). This method differs from the prior art where cell lysis and luciferase addition was conducted in a step-wise manner. See specification, page 3, lines 29-30. "[C]urrent assays that use luminescence to detect ATP are handicapped by the need for successive, time-consuming steps." Specification, page 4, lines 6-7.

The single step assay of the present invention is possible because Applicants have discovered a class of luciferases which are stable to enzymatic degradation. Hence,

claim 1 has been amended to require that the "reagent composition maintains at least about 30% activity, as measured by luminescence after the reagent composition is combined with the sample, for at least one hour compared to the reagent composition's activity just after the luciferase is combined with the one or more detergents."

CLAIM REJECTIONS

In the Office Action, the Examiner rejected Claims 1-64 and objected to Claims 15, 18, 30, 42 and 59-64. However, Applicants respectfully assert that none of the claims are either anticipated or obvious and all of the claims are allowable.

35 U.S.C. § 102

Claims 1-14, 16-17, 19-29, 31-41 and 43-58 are rejected under 35 U.S.C. § 102(b) over Simpson et al. The Office Action states, "Simpson et al. disclose a bioluminescent method for assaying of ATP in a sample by contacting a reagent composition comprising a cationic surface active agent to the sample, adding an amount of non-ionic surface active agent, *followed by* determining the ATP released into the sample using the luciferase-luciferin reagent." (*Citing,* Simpson, column 6, lines 53-68 and column 7-8; lines 1-18; *emphasis added*). Office Action, page 3.

However, as this cited portion from Simpson demonstrates, Simpson requires the *step-wise* addition of reagents, and does not teach or suggest the addition of a detergent and a luciferase. Simpson teaches *the step-wise, separate* addition of the ATP releasing agent (cationic detergent) and neutralizing agent (nonionic detergent) throughout their specification. See e.g. Simpson, column 3, lines 10-15 & 32-50; column 4, lines 1-4. Further, Simpson teaches the step-wise addition of detergent first, followed by the use of a luciferase-luciferin reagent ("and *thereafter* determining the ATP released into the sample using the luciferase-luciferin reagent," Simpson, claim 1, line 58-60 (*emphasis added*)).

Argument

Applicants respectfully disagree with the Examiner. Nowhere does Simpson teach nor claim a reaction in which cationic detergent, nonionic detergent, and luciferase-luciferin reagents are *simultaneously* added to the sample to be assayed.

The Examiner asserts that Simpson discloses a reagent composition comprising both a cationic surface active agent and a non-ionic surface active neutralizing agent. (*citing* Simpson, Column 3, line 16-19). Office Action, page 3. However, the cationic surface active agent and non-ionic surface active agent in Simpson are added to the assay in separate steps. The assay is to be performed by contacting the cellular ATP source "with ATP releasing agent and contacting *the resultant solution* with a neutralizing agent" Simpson, column 3, lines 13-14. (With the releasing agent preferably a cationic surface agent and the neutralizing agent a non-ionic surface active agent. Simpson, column 3, lines 16-19.) Again, Simpson fails to set forth the one step addition of cationic detergent, nonionic detergent, and luciferase-luciferin reagents.

The Examiner contends that Simpson also discloses combinations of cationic surface active agents, ionic detergents, and non-ionic detergents. *Citing* Simpson, column 2, lines 1-68. Office Action, page 4. But Simpson only refers to these agents in conjunction with discussions of the problems inherent in their use. Simpson notes that cationic surface active agents reduce the precision of the ATP assay (Simpson, column 2, lines 30-40) and that a mixture of ionic detergents requires dilution prior to performing the assay, and that non-ionic detergents may distort the kinetics of the luciferase assay (Simpson, column 2, lines 41 to column 3, line 7). In view of the problems with the use of detergents, Simpson is better said to teach away from the addition of cationic surface active agents, ionic detergents, and non-ionic detergents in a single step of an ATP assay.

The Examiner also contends that Simpson anticipates the present application when it teaches the use of EDTA (column 3, lines 8-68 and column 4, lines 1-68). Office Action, page 4. The Examiner finds anticipation when Simpson et al. teach the use

of a cationic detergent at the concentration of 0.1% (w/v) or greater and the use of the detergents used in the present application's claim 14. However, again, in Simpson EDTA and these detergents are *not simultaneously added* to the sample with luciferase in a *single* step.

The Examiner concedes that the present application's Claim 1 limitation that "the reagent composition is capable of maintaining at least about 30% activity, as measured by luminescence after the reagent composition is combined with the sample, for at least one hour" is not disclosed by Simpson. Office Action, page 4. However, the Examiner contends that this element's disclosure is "an inherent property of the reaction mixture in the ATP assay disclosed by the Simpson et al. reference because Simpson et al. disclose methods that use the same starting materials and reaction conditions claimed in the present invention." Office Action, page 4.

Anticipation under 35 U.S.C. § 102 requires that each and every element be set forth in a single prior art reference. MPEP § 2131 (8th ed. 2001); *Verdegaal Bros. v. Union Oil Co. of Calif.,* 814 F.2d 628, 631 (Fed. Cir. 1987). The express, implicit or *inherent* disclosures of a prior art reference may be relied upon for a rejection of claims under 35 U.S.C. § 102. MPEP § 2112 (8th ed. 2001); *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995). However, the Examiner must provide a basis in fact or technical reasoning to reasonably support the contention that the allegedly inherent characteristic *necessarily* flows from the teachings of the prior art. MPEP § 2112 (8th ed. 2001); *Ex parte Levy,* 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). It is not enough that a result or characteristic may occur or be present in the prior art to establish inherency. MPEP § 2112 (8th ed. 2001); *In re Rijckaert,* 9 F.3d 1531, 1534 (Fed. Cir. 1993).

Simpson does not explicitly disclose any data on a luciferase reaction monitored for more than a few seconds. (*See, e.g.,* Fig. 2 Simpson.) Moreover, the reaction conditions are different in Simpson from the present application because Simpson teaches the *multi-step* addition of reagents in its ATP assay. Therefore, it is not clear

that a process that maintains 30% of the luciferase activity after one hour *necessarily* flows from the teachings of Simpson. Thus, Simpson does not anticipate any of the claims of the present application.

Furthermore, Examples 3 and 7 of the present application suggest that Simpson does not anticipate the present invention. Example 3 of the present application is similar to Example 1 of Simpson. Both examples disclose the degree of luciferase stability in the presence of cationic detergent after various times and in various concentrations of the cationic detergent. Simpson's Figure 1 demonstrates that the cationic detergent benzethonium chloride causes a decrease in the luciferase enzyme's activity (measured by light intensity decay versus starting light intensity) of up to 600% per minute (at 0.05% benzethonium chloride w/v). The present application discloses assay conditions where a wild-type luciferase enzyme ("LucPpy" in Table J) in the presence of 0.02% (w/v) of the cationic detergent dodecyltrimethylammonium bromide (DTAB) retains 99.53% of its activity (as measured by luminescence generated in response to ATP) after 34 minutes. Specification, page 51, Table J.

In addition, using a genetically engineered luciferase ("LucPpe2m146" in Table J), the present application discloses assay conditions in which a substantial amount of the luciferase activity and luminescence is retained after addition of the cationic detergent DTAB. Specification, page 51, Table J.

Similarly, the present application's Example 7 demonstrates that luciferase stabilization is not achieved in Simpson's assay. The reaction mixture disclosed in the present application maintains luciferase activity even in the presence of DTAB over the course of 325 minutes (Specification, Page 60, Table Q, which discloses luciferase activity half-lives ranging from 1.4-14.2 hours) while Simpson's Figure 1 demonstrates that the cationic detergent benzethonium chloride causes light decay of up to 600% per minute (a luciferase activity half-life of less than one minute). Thus, Simpson does not teach an assay with the properties of enhanced luciferase stability disclosed in the present application and Simpson does not anticipate the

present application's claim elements requiring the maintenance of at least about 30% activity for at least one hour.

37 C.F.R. 1.132 Declaration

Alternatively, the Declaration under 37 C.F.R. 1.132 enclosed herewith, and signed by inventor Keith Wood, overcomes the asserted basis for this rejection. Specifically, the Declaration provides that according to the specification as filed, "[t]here are no ATP detection systems that provide a composition or method capable of inactivating endogenous ATPase activity and detecting luciferase activity in the same environmental milieu. Therefore, current assays that use luminescence to detect ATP are handicapped by the need for *successive, time-consuming steps*." (Specification of Application Serial No. 09/813,279, as filed on March 19, 2001, at page 3, line 29 – page 4, line 7, emphasis added). The Declaration further notes that according to the specification, unlike the prior art, the present invention does indeed provide "methods... to detect ATP in a sample by reducing the steps of cell lysis, endogenous ATPase inhibition, and substrate and luciferase addition *to a single step* that is then followed by detection of the resulting luminescence." (Specification of Application Serial No. 09/813,279, as filed on March 19, 2001, at page 10, lines 7-10, emphasis added).

Applicants respectfully contend that the asserted basis for this rejection has been obviated in light of either the above arguments, or the enclosed Declaration. Reconsideration and removal of the rejection is requested.

35 U.S.C. § 103

The Examiner alternatively contends that Simpson renders the present application's claims 1-8 obvious under 103(a).

Argument

To make a *prima facie* case of obviousness, the Examiner must first show there is suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Importantly, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. MPEP § 2143 (8th ed. 2001); *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Simpson fails to suggest the combined addition of all the detergents and luciferase reagents. Instead, as discussed above, Simpson teaches away from such a combined addition of detergent with luciferase reagents.

The present invention is not obvious because it discloses an assay that allows the addition of detergents and luciferase in a single step. The disclosed one-step assay is possible because the reagent composition disclosed has properties of enhanced stability. In addition, in the present application's reagent composition, luciferase is resistant to the effects of the ATPase inhibitor also present in the reagent composition. Specification, page 4, line 23-27.

Nothing in Simpson suggests that the combination of cell lysis, the inhibition of endogenous ATPase, and substrate and luciferase addition to a single step will be successful. Simpson does state that the "careful manipulation of the ratio of one surface active agent to the other... could limit (but not eliminate) the decay" of the luciferase reaction rate. However, Simpson follows by warning that these agents reduce the assay precision. Simpson, column 2, lines 35-40. Thus, the prior art does not offer a reasonable expectation of success for a modification of the prior art constituting the invention claimed in the present application.

37 C.F.R. 1.132 Declaration

Alternatively, the Declaration under 37 C.F.R. 1.132 enclosed herewith, and signed by inventor Keith Wood, overcomes the asserted basis for this rejection. For the reasons discussed above, Applicants assert that it would not have been obvious at the time of the invention to provide a one-step assay.

The present invention is not obvious in light of Simpson because Simpson teaches away from a one-step ATP assay. In contrast to the teachings of the specification recited in the Declaration, Simpson teaches away from the desirability of a one-step assay. More specifically, Simpson discusses the reduced effectiveness of the luciferin-luciferase reagent if combined with detergents, rather than being used in a subsequent step after neutralizing the releasing agent. For example, as noted above, Simpson teaches that cationic surface active agents reduce the precision of the ATP assay (Simpson, column 2, lines 30-40) and that a mixture of ionic detergents requires dilution prior to performing the assay, and that non-ionic detergents may distort the kinetics of the luciferase assay (Simpson, column 2, line 41 to column 3, line 7). In view of the problems with the use of detergents, Simpson is better said to teach away from the addition of cationic surface active agents, ionic detergents, and non-ionic detergents in a single step of an ATP assay.

Reconsideration and removal of the rejection is requested.

35 U.S.C. § 112, 2nd ¶

The Examiner rejected claims 1-64 for being indefinite under 35 U.S.C. § 112, second paragraph. Specifically, the Examiner asserts that the recitation of the phrase "reagent composition is capable of maintaining..." are "open ended," and do "not describe a definite activity." Office Action, page 2.

Applicants respectfully disagree, but have elected to amend the claims to facilitate prosecution and place the claims in better condition for appeal.

Applicants note that the original claim language directed to a reagent composition "capable of maintaining" is sufficiently definite in its plain meaning, and as read in light of the specification. For example, the specification at page 13, lines 1-13, page 26, lines 19-32, and subsequent examples, provide non-limiting examples of methods of the invention that are "capable of maintaining at least about 30% activity."

Based on the above amendments to the claims, Applicants respectfully submit that the basis for this rejection has been obviated. Reconsideration and removal of this rejection is requested.

CONCLUSION

Applicants believe that currently pending Claims 1-64 are patentable. Applicants respectfully request that the Examiner grant early allowance of this application. The Examiner is invited to contact the undersigned attorney for the Applicants via telephone if such communication would expedite this application.

Respectfully submitted,

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